ARGUMENT SCHEDULED FOR APRIL 17, 2025

No. 24-5235

IN THE

United States Court of Appeals for the District of Columbia Circuit

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff-Appellant,

v.

ROBERT F. KENNEDY, JR., *et al.*,

Defendants-Appellees.

On Appeal from the United States District Court
for the District of Columbia, No. 24-cv-02234
(Dabney L. Friedrich, J.)

FINAL REPLY BRIEF FOR PLAINTIFF-APPELLANT

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March 4, 2025

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REGULATIONS:

GLOSSARY

APA	Administrative Procedure Act
FDA	Food and Drug Administration
MSN	MSN Pharmaceuticals Inc.

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INTRODUCTION AND SUMMARY OF ARGUMENT

The rules governing generic drug approval are built on a baseline assumption: The drug must be the same as the innovator product FDA has already determined to be safe and effective for its intended use. Because FDA does not do any testing itself, and the generic drug applicant does only limited human testing, the sameness requirement allows the public to have confidence in generic drugs. For the same

reason, it is critical that the labeling for a generic drug be the same as that for a brand-name drug. Any differences must not render the generic *any* less safe or effective than the reference product.

Over time, Congress by statute and FDA even more by regulation have adopted narrow exceptions to that general scheme. This appeal comes on the heels of FDA's attempt to stretch those narrow exceptions beyond what federal law permits. FDA remains bound by the "same-labeling" and "same-active-ingredient" requirements that have governed generic drug approvals for decades. That remains true even in light of the Government's interest in fulfilling the broad purposes of the Hatch-Waxman amendments or its policy goals favoring generic drugs.

In approving MSN Pharmaceuticals Inc. (MSN)'s purported generic referencing Novartis's product ENTRESTO, FDA flouted those sameness requirements. FDA's action cannot survive judicial review for three reasons.

I. For one, the labeling of MSN's purported generic lacks critical safety instructions that FDA itself found result in fewer clinically relevant adverse events for a vulnerable patient group. FDA insists that the MSN product is "not unsafe" with the carve-out, despite the agency having concluded the safety information was important enough to add to ENTRESTO's labeling. FDA argues that it is unknown whether ENTRESTO's modified dosing regimen "is the safest and best-tolerated option" for these patients. FDA Br. 25, 39. But that is not the standard. The standard

is whether the generic is *any less* safe, not whether the resulting labeling renders the product the safest in all situations. And FDA has not met its obligation to provide a reasoned analysis for its action.

II. FDA has a separate same-labeling problem: FDA has not just carved out a protected indication from inclusion on the generic's labeling. It has instead *rewritten* out of whole cloth ENTRESTO's indication for the generic. The agency's governing statute and regulations require generic drugs and their reference products to bear the same labeling because that is what ensures consistent, safe, and effective use of the two products. That requirement is not "a word game." FDA Br. 34. It is the law.

III. Finally, the MSN product lacks the same active ingredients as ENTRESTO. When FDA approved ENTRESTO, the agency observed that it is comprised of two active moieties combined into a singular complex. According to FDA and MSN, MSN's active ingredients are a physical mixture of separate valsartan disodium and separate sacubitril sodium. So FDA has changed its tune and now characterizes ENTRESTO's active ingredients as two salts, *see* FDA Br. 47, in an eleventh-hour bid to circumvent its own regulations. But it cannot. FDA itself has recognized that ENTRESTO's complexed active ingredients are chemically distinct from a physical mixture and cannot establish that these active ingredients are the same as the generic's.

Each of these three failures independently renders the agency's approval of MSN's generic unlawful under the APA. The District Court was wrong to conclude otherwise, and this Court should set aside FDA's unlawful action.

ARGUMENT

I. FDA WRONGFULLY CARVED OUT CRITICAL SAFETY INSTRUCTIONS FROM THE GENERIC'S LABELING.

FDA may approve a labeling carve-out for a generic drug product to address statutory marketing exclusivity or patent rights. 21 C.F.R. § 314.127(a)(7). But the agency must ensure that the carve-out does not render the generic any "less safe or effective." *Id.* FDA failed to meet that basic duty in excising critical safety instructions from the MSN generic's labeling.

A. FDA Failed To Determine That The Dosage Carve-Out Renders The MSN Product No Less Safe Or Effective Than ENTRESTO.

ENTRESTO's instructions outline a modified dosing regimen for a patient group including: (1) ACE inhibitor or ARB-naïve patients and (2) patients who were previously taking low doses of these agents before starting on ENTRESTO. JA771 [AR 1471]. These instructions alert patients and providers that the standard regimen could put this patient group at risk and set forth a modified dosing regimen demonstrated in a clinical trial to reduce the number of adverse events for such patients. Accordingly, FDA determined that these instructions were appropriate for ENTRESTO "from a safety perspective." JA623 [AR 311]. Yet the agency

approved labeling for MSN's generic that omits the modified dosing regimen, even though this carve-out was based on no new safety or efficacy data or information. JA111–112.

Searching for a way to rationalize the agency's about-face, the Government and MSN try to water down FDA's determination that the modified regimen reduces the risk of adverse events for the relevant patient population and inclusion of the regimen on ENTRESTO's labeling. For its part, the Government contends that it determined that the modified regimen "was reasonable," not that it "was so important that any deviation from the regimen raised safety or efficacy concerns." FDA Br. 40–41. For one, FDA acted deliberately—and within its regulatory authority—when it approved ENTRESTO's labeling with the modified dosing regimen. And FDA has, once again, confused the standard. It is not whether excising the modified dosing regimen renders the drug *so* much less safe or effective as to present safety or efficacy concerns. Nor is it whether the TITRATION study was "necessary" for ENTRESTO's approval in the first place. FDA Br. 43 (quoting JA133). The standard is whether a labeling carve-out renders the proposed generic drug *any* less safe or effective.

MSN similarly suggests that when FDA deemed the regimen "reasonable," it merely meant that "it couldn't hurt." MSN Br. 12. But that is not a basis for FDA to add language to a product's labeling. In approving the inclusion of the modified

regimen on the labeling, FDA did not deem it to have only a neutral impact on safety or efficacy. It found that it would reduce the risk of adverse effects, based on the TITRATION study's finding that it made a "major difference[]" in the incidence of hyperkalemia (high blood potassium levels). JA621 [AR 301]. In other words: The modified regimen makes usage of the drug safer for vulnerable patients. By definition, omitting it will make the product *less* safe for these patients. That is why FDA approved its inclusion in ENTRESTO's labeling in the first place.

MSN also points to FDA's approval of the dosage carve-out, claiming that FDA's "detailed technical analysis" concluded "that it is '*unknown*' " whether the modified regimen is "any safer" for ACE inhibitor or ARB-naïve patients. MSN Br. 12 (emphasis added in original). That is wrong. FDA stated that it is "unknown" whether the modified dosing regimen "is the *safest* and *best-tolerated* option" but noted that TITRATION suggested the target patient group—ACE inhibitor or ARB-naïve patients, and patients on low doses of these agents—may benefit from a modified regimen that increases their tolerability and reduces their risk of experiencing adverse reactions. JA355 [AR 3949]. And in any event, if by 2024 it was truly "unknown" to FDA whether its 2015 decision to approve the modified dosing regimen conferred valuable safety benefits to vulnerable patients, that would counsel in favor of maintaining its earlier judgment—not keeping it in place for ENTRESTO while at the same time reversing it for a competing generic.

B. FDA's Departure From The Modified Dosing Regimen Is Unlawful And Must Be Set Aside.

FDA's actions must at all times be "reasonable and reasonably explained." *Pharmaceutical Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 262 (D.C. Cir. 2020). This standard requires FDA to "give a 'reasoned analysis' to justify the disparate treatment of regulated parties that seem similarly situated" and that FDA's reasoning not be "internally inconsistent." *ANR Storage Co. v. FERC*, 904 F.3d 1020, 1024 (D.C. Cir. 2018) (citing *Sierra Club v. EPA*, 884 F.3d 1185, 1194–1196 (D.C. Cir. 2018)). FDA failed to satisfy that requirement here. There is a complete contradiction between the agency's applications of the TITRATION study's results to ENTRESTO and MSN's generic, and FDA and MSN cannot reconcile these conflicting positions.

The agency concluded that the modified regimen was appropriate "from a safety perspective" for ENTRESTO. JA623 [AR 311]. It acknowledged as much in approving the dosage carve-out for MSN's generic, explaining that TITRATION supports ENTRESTO's modified dosing regimen for the relevant patient group because of its potential to increase tolerability and reduce the risk of adverse events. JA355–356 [AR 3949–3950]. Yet, to justify the carve-out, FDA now states that the study results "do[] not provide a scientific basis to conclude . . . that the standard Entresto dosing regimen puts such patients at a greater risk of adverse reactions."

FDA Br. 40 [quoting JA356 [AR 3950]). FDA fails to explain how the same study results could both provide both [1] a basis and [2] no basis at all to conclude that the risk of adverse reactions for the target patient population is higher under the standard dosing regimen. Nor does the agency explain how carving out a modified regimen that may increase drug tolerability and reduce the risk of adverse effects makes a drug *no* "less safe or effective"—not even by the slimmest of margins.

MSN, for its part, conflates the length of FDA's analysis with its soundness, stating that FDA's "300 pages of analysis" "surely meets the requirements for a reasonably explained decision." MSN Br. 17. But sheer page volume does not render a decision reasonable. Among other things, to be reasonable, FDA's analysis must be internally consistent. *See Gulf Power Co. v. FERC*, 983 F.2d 1095, 1101 (D.C. Cir. 1993) ("[W]hen an agency takes inconsistent positions, as FERC did here, it must explain its reasoning."). That FDA could not reconcile its conflicting positions on what the TITRATION study demonstrates in 300 pages is a powerful tell. This unexplained inconsistency is exactly the kind of arbitrary and capricious agency judgment that warrants this Court's review.

FDA points to Section 5 of MSN's labeling as another reason this Court should not scrutinize FDA's approval of the carve-out. According to FDA, the safety instructions in Section 5, which direct providers on the course of treatment *after* a patient has suffered an adverse event, are "sufficient" to "adequately

manage[]" the risk of adverse reactions. JA357 [AR 3951]; *see* FDA Br. 16. But post-hoc instructions on *managing* an adverse event after it occurs are wholly different from instructions on decreasing the starting dosage to *reduce the risk* of adverse events and avoid them happening in the first place. It is not reasonable that FDA would allow patients to first suffer and then try to manage the fall-out, versus retain instructions to prevent the injury at all.

FDA's regulations require any language that implies or suggests modifying dosing regimens to be made in the dosing section of a product's labeling—not in some other section of the labeling. 21 C.F.R. § 201.57(c)(3)(ii). FDA suggests that this argument was waived below. FDA Br. 42–43. That is not true: Novartis repeatedly raised this argument in briefing and at argument below. *See* JA98 ("The agency's own regulations also make clear that Section 2 of a product's labeling 'must' include modified dosing regimens in special populations; '[d]osing regimens must not be implied or suggested in other sections of the labeling if not included in this section.' 21 C.F.R. § 201.57(c)(3)(ii)."); JA105–106 [Tr. 27:21–28:01] (Novartis counsel explaining that "what FDA has come back and said is, it's okay to remove the modified dosing regimen from Section 2 of the drug label, which is where all dosing regimens have to go. There's actually an FDA regulation that prohibits a label from containing references to a dosing regimen that aren't included in Section 2.").

It's not hard to see why the Government hopes to sidestep the regulation: FDA's primary response to Novartis's well-documented objection to the agency's decision to drop the modified dosing regimen from the MSN labeling is that the labeling *elsewhere* cues healthcare providers to make dosing modifications. JA356 [AR 3950]. But FDA's own regulations make clear that any dosing modifications for vulnerable populations must appear in Section 2 of the labeling. The agency has left providers with incomplete dosing instructions in Section 2 of the MSN product labeling. When FDA defends this action by claiming that dosing-modification information can be conveyed someplace else in the labeling, its action violates its own regulations. 21 C.F.R. §§ 201.57(c)(3)(ii), 201.57(c)(2)(i)(D).

What's more, the standard is not whether the carve-out would render the drug *unsafe* or *ineffective*; it is whether the carve-out would make the drug *any less* safe or effective. FDA and MSN argue that the Section 5 instructions are "*adequate* for safety and efficacy." MSN Br. 19 (emphasis added); FDA Br. 42 (stating Section 5 would give health care providers "adequate" dosing information). They pointedly do not assert, however, that excluding the modified dosing regimen for the generic, and relying only on the Section 5 instructions, renders the generic "no less" safe and effective. *See* FDA Br. 41–43; MSN Br. 18–20. (Per FDA, it is "unknown" whether the modified dosing regimen is the "safest and best-tolerated option" for the special patient population.) JA355 [AR 3949]. FDA instead claims that Sections 5.3

through 5.5 of the labeling "make clear that dose reduction may be warranted" to mitigate the risk of adverse events. FDA Br. 41–42. Again, these sections describe reducing the dosage only after adverse effects arise. JA68.

But reducing the dosage *after* a patient has started experiencing adverse reactions is plainly not the same thing as preventing the adverse reactions in the first place. To the extent FDA suggests that Sections 5.3 through 5.5 inform a provider that it may be appropriate to start at patient a lower dosage and uptitrate, only Section 5.3 (concerning hypotension) makes any reference to *starting* at a lower dose. JA68. And it does so in reference to volume- and salt-depleted patients—patients taking high doses of diuretics—not ACE inhibitor or ARB-naïve patients or patients on a low dose of these agents. JA68.

The dosage carve-out poses real harm to vulnerable patients, depriving them and their providers of critical safety instructions. FDA needed to explain and show that the carve-out will not render the generic any less safe or effective than ENTRESTO. It did neither. FDA's action violates the APA, and this Court should set aside the agency's approval of MSN's product.

II. THE MSN PRODUCT DOES NOT SHARE THE SAME INDICATION AS ENTRESTO.

A. FDA Must Abide The Statute's Same-Labeling Requirements.

Under the FDCA, a generic drug and its labeling must be "the same as" the brand-name drug that its ANDA references. 21 U.S.C. § 355(j)(2)(v). FDA granted

itself a narrow exemption to approve labeling for products marketed by "different manufacturers," 21 C.F.R. § 314.94(a)(8)(iv), and the Government tests the scope of that exception by claiming that it extends to significant labeling differences beyond a different manufacturer, product name, or company address. JA322–324 [AR 3916–18]. Assuming this interpretation can be described as the best reading of the FDCA, the statute does not permit FDA to read the same-labeling requirement out of the law entirely. *United States Sugar Corp. v. EPA*, 113 F.4th 984, 991 (D.C. Cir. 2024) ("[W]e must apply what we regard as the statute's 'best reading' " (quoting *Loper Bright Enters. v. Raimondo*, 603 U.S. 369, 392 & n.4 (2024)). From the early days of the Hatch-Waxman Amendments, FDA has "emphasize[d] that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited." 54 Fed. Reg. 28,872, 28,884 (July 10, 1989).

Precedent does not help the Government on the same-labeling point either. FDA's reliance on *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), proves a critical point: A generic manufacturer may either "file a so-called paragraph IV certification" challenging the validity or infringement of patents covering the brand-name drug—or it may "submit a so-called section viii statement," where generic company may "market the drug for one or more methods of use not covered by the brand's patents." *Id.* at 406–407. *Caraco* explains that the availability of that latter pathway—the one MSN chose—turns on the FDA-

approved labeling of the brand-name product. *See id.* at 407. Underscoring this point, ENTRESTO's current labeling *is FDA's brainchild*. *See* JA865–866 [AR 4012–4013]. Novartis sought approval for different labeling that would have included two indications in heart failure, for both reduced and preserved ejection fraction. It was *FDA* that required the current ENTRESTO labeling with only one indication. JA865–866 [AR 4012–4013]. After approving the innovator product, the agency must stand by its earlier judgment when it comes to generics.

The Government and MSN argue that this Court's decision in *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), grants FDA authority to make more sweeping changes to drug labeling than the FDCA's text would suggest. FDA Br. 29–31, MSN Br. 21–22. Even assuming the opinion's "legal analysis remains binding on this Court," FDA Br. 31, that analysis dealt with FDA's effort to remove one of several indications from generic labeling, and it necessarily stopped short of the question presented here. In this case, FDA has dissected out a single indication in the innovator drug and then approved that fragmented version as part of a generic drug's labeling. To read *Bristol-Myers Squibb* as somehow blessing that sort of gambit—a move no court has ever endorsed as a permissible labeling carve-out, JA351 [AR 3945]—is to bend the decision beyond its breaking point.[1]

[1] MSN, like the District Court, offers just one counterexample: An FDA adjudicative decision, never challenged in court, where the agency fashioned an indication

The record shows that as of 2021, FDA no longer relied on ejection fraction as a strict diagnostic criterion for heart-failure patients, reflecting the consensus in the scientific community that no longer divided patients into camps based on a measure of reduced or preserved ejection fraction. JA791 [AR 1491]. And yet the labeling that FDA approved for MSN reverts back to this outdated modality, stating that MSN's "Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure *and reduced ejection fraction*." JA67–68 (emphasis added). So when FDA and MSN point to agency review documents that profess to show the agency really did consider ENTRESTO's current labeling, FDA Br. 31–33, MSN Br. 27–30, those assurances must be evaluated against the indication statement that FDA actually approved for the MSN product—which resurfaces the old "reduced ejection fraction" measure. JA67–68. The proof is in the labeling.

B. Omission Does Not Imply Addition.

FDA has interpreted the FDCA to permit labeling carve-outs on a limited basis, setting out in the operative regulation that "[s]uch differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or

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statement by combining two mutually exclusive subsets of a single patient population. MSN Br. 25–26. To describe this agency action is to distinguish it. *See* Novartis Br. 50.

pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act." 21 C.F.R. § 314.94(a)(8)(iv).

Novartis explained in its opening brief that this regulation shows that FDA knows how to, and in fact did—in the very regulation the agency uses to approve labeling carve-outs—distinguish between "labeling revisions" and an "omission." Novartis Br. 45–46. The text and structure of 21 C.F.R. § 314.94(a)(8)(iv) confirm that "omission," the ordinary meaning of which does not embrace the concept of addition, should not be read to mean the same thing as "revisions," a term that may be fairly read to include deletions. Given that FDA used these distinct terms in the exact same regulation, opting to permit "revisions" when dealing with adjustments required to conform to "FDA labeling guidelines or other guidance"—but reserving labeling "omissions" for carve-outs "of an indication or other aspect of labeling"—the Court should give effect to that choice. *See UPMC-Braddock Hosp. v. Sebelius*, 592 F.3d 427, 438 (3d Cir. 2010) ("[T]he regulation explicitly refers to a 'surviving' corporation, indicating that the agency knew how to refer to the surviving, post-merger entity if it wanted to.").

Neither the Government nor MSN offers any response to this textual argument. They offer no contrary reading of the regulation whatsoever, giving no

reason to conclude that the narrower term "omission" must be synonymous with "revision." Instead, the Government pillories adherence to FDA's regulatory command as a "word game." FDA Br. 34 (accusing Novartis of "elevating stylistic decisions over [] substance"). In the world of drug labeling, though, the words chosen for the labeling *are* the substance. It is thus imperative that FDA heed the requirements of its own binding regulation, even if the agency believes that the regulation's dictated "outcome is at odds with one of the fundamental purposes of the Hatch-Waxman Amendments[,] to speed generic competition." FDA Br. 34; *see also* MSN Br. 2 (urging an interpretation that advances the project of "skinny labeling").

In an APA case involving the application of an agency's regulation, however, the reviewing court's "task is not to decide which among several competing interpretations best serves the regulatory purpose," *Trinity Broad. of Fla., Inc. v. FCC*, 211 F.3d 618, 625 (D.C. Cir. 2000); instead, "the court must give effect to the regulation's plain meaning." *Statewide Bonding, Inc. v. U.S. Dep't of Homeland Sec.*, 980 F.3d 109, 116 (D.C. Cir. 2020). Here, that means concluding that omission means omission, not addition.

As Novartis has explained, when FDA approved the MSN labeling, it reverse-engineered labeling that FDA had never before approved for Novartis.[2] That was unlawful under FDA's governing statute and binding regulations. Novartis Br. 40–41, 47–48. It also was arbitrary and capricious because the agency at no point provided a reasoned explanation for its action or justified its divergent approach to the MSN product, despite FDA's acknowledgment that no new data or developments had emerged in the intervening period. JA111–112.

III. THE MSN PRODUCT DOES NOT HAVE THE SAME ACTIVE INGREDIENTS AS ENTRESTO.

To satisfy the same-active-ingredient requirement, ENTRESTO and MSN's generic must contain "identical amounts of the identical active drug ingredient, i.e., *the same salt or ester of the same therapeutic moiety*[.]." 21 C.F.R. § 314.3(b). The District Court concluded that ENTRESTO and MSN's generic share the same active ingredients, despite the fact that the active ingredients of ENTRESTO are complexed and the active ingredients of MSN's generic purportedly are not. The court reached this conclusion by deferring to FDA's late-breaking revelation that both drugs contain a "sacubitril sodium" salt and a "valsartan disodium" salt. JA135. On

[2] ENTRESTO's original statement reflected its FDA approval to treat heart failure in patients with chronic heart failure and reduced ejection fraction, but lacked a statement instructing physicians to use clinical judgment rather than rely on measurement of ejection fraction. JA552 [AR 19].

appeal, both FDA and MSN take a similarly expansive view of active ingredient sameness. FDA Br. 46–48; MSN Br. 34. That misses the mark.

FDA argues that ENTRESTO and the generic have the same active ingredients because they contain sacubitril anions, valsartan anions, and sodium cations in the same ratio. FDA Br. 46. Similarly, MSN reasons that because both ENTRESTO and MSN's generic contain anionic forms of sacubitril and valsartan, and sodium cations, in a 1:1:3 ratio, they "exist as the 'same salt.'" MSN Br. 34. But just because the separate constituents are the same does not mean that the combined result is also the same. Yes, both products contain sacubitril anions, valsartan anions, and sodium cations, but that does not mean they contain the same active ingredients.

FDA correctly observes that "sacubitril sodium" is "the salt formed by combining the anionic form of sacubitril with a sodium cation" and "valsartan disodium" is "the salt formed by the anionic form of valsartan with two sodium cations." FDA Br. 47. That is true, as far as it goes. But FDA then suggests that any compound containing sacubitril and valsartan anions and sodium cations in a 1:1:3 ratio contains the separate salts sacubitril sodium and valsartan disodium. *See id.* That is *not* true. The ENTRESTO complex does not contain separate sacubitril sodium and separate valsartan disodium; instead, ENTRESTO contains a singular

structure composed of sacubitril and valsartan anions in ionic coordination with sodium cations. JA555 [AR 58].

In 2015, FDA recognized that ENTRESTO meets the definition of a complex, because all of the components are bound together in a single formation. JA555 [AR 58]. It is a single structure formed by sacubitril anions and valsartan anions in association with sodium cations, but it does not form the same two discrete salts that purportedly constitute MSN's product.

MSN claims that FDA disagreed with using the term "sodium salt complex" to refer to ENTRESTO's active ingredients. MSN Br. 34 (citing JA555 [AR 58]). MSN is off base. Again, the agency made clear that the chemical nature of ENTRESTO's active ingredients meets the definition of a singular complex and that its chemical structure is akin to a salt. JA555 [AR 58]. And at no point in the record prior to its 2024 petition response did FDA ever characterize this structure as a physical mixture of two salts.

Only MSN makes much of the fact that FDA considers ENTRESTO to be a fixed-dose combination product. MSN Br. 36. But for fixed-dose combination products, FDA requires generic applicants like MSN to show that their generic product contains the same chemical form of each active ingredient in the reference drug. JA159 [AR 2801]. A physical mixture of valsartan disodium and sacubitril sodium is chemically different from the ENTRESTO complex. *See* JA555 [AR 58];

JA637–638 [AR 810–811]. MSN maintains that "both FDA and Novartis consistently identified ENTRESTO as a 'sodium salt complex'" and that "[t]he same is true for MSN's product." MSN Br. 30. Yet of the 16 instances in the administrative record where the phrase "sodium salt complex" is used, 15 refer to ENTRESTO, and only 1 refers to MSN's generic—hardly a consistent practice of classifying the generic as a "sodium salt complex."

MSN also insists that its product is not a physical mixture of two separate active ingredients. But MSN had asked FDA if it would accept a generic formulation containing "a physical mixture" of sacubitril and valsartan in a 1:1 ratio. JA819 [AR 2347]. FDA responded that it would and that MSN need not compose the generic using the same complex found in ENTRESTO. JA819 [AR 2347]. So MSN's generic purportedly contains a physical mixture of two separate salts, and ENTRESTO contains a complex. MSN then tries to obscure FDA's inconsistent characterization of ENTRESTO's active ingredients as a "scientific determination." MSN Br. 40. But the agency's obligation to act reasonably and reasonably explain its actions is not eliminated because its determination involved matters of chemistry. FDA's internally inconsistent reasoning for its active ingredient sameness finding cannot be reasonable. *ANR Storage*, 904 F.3d at 1024 (D.C. Cir. 2018) (citing *Sierra Club*, 884 F.3d at 1194–1196).

ENTRESTO and MSN's generic may both contain sacubitril, valsartan, and sodium, but that does not mean they have the "same" active ingredients under the law. At the eleventh hour, FDA has reversed itself and convoluted the sameness requirement to bring MSN's generic to market. That is unlawful. This Court should not condone FDA's approval.

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The Court's January 16 decision directed that oral argument be set in this appeal for the first available date following the completion of briefing. Counsel appreciates the Court's accommodation, particularly in light of the July 15, 2025 expiry of ENTRESTO's remaining exclusivity period.

CONCLUSION

For the foregoing reasons, as well as those stated in Novartis's principal brief, the District Court's judgment should be reversed.

Respectfully submitted,

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March 4, 2025

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g)(1), the undersigned hereby certifies that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B)(i).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f), the brief contains 4,722 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word for Office 2010 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g)(1), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

/s/ Catherine E. Stetson
Catherine E. Stetson

March 4, 2025

CERTIFICATE OF SERVICE

I certify that on March 4, 2025, the foregoing was electronically filed through this Court's CM/ECF system, which will send a notice of filing to all registered users.

/s/ Catherine E. Stetson
Catherine E. Stetson